REMARKS

FORMAL MATTERS:

Claims 1-24 are pending after entry of the amendments set forth herein.

Claims 4-12 and 17-24 are withdrawn from consideration.

Claims 1-3, 13-16 were rejected.

Claim 15 has been amended. Support for the amendment is found in the claims as originally filed and throughout the specification at, for example, page 20, paragraph [0078].

Accordingly, no new matter has been added.

LINKING CLAIMS 1, 13-16

Applicants express gratitude in examiners indication that Claims 1 and 13-16 are linking claims and should be examined together with the elected invention.

The following remarks have been supplemented from the response filed on June 21, 2004, in order to take into consideration the newly applied rejections.

REJECTIONS UNDER §112, ¶2

Claims 3, 15, and 16 were rejected as being indefinite. Each aspect of this rejection is addressed below.

Claim 3

"binding to a surface structurally defined by . . . residues 342 and 349"

The Office has rejected claim 3 for recitation of the above phrase on the grounds that it is not clear "under which conditions the residues (that are flexible) identify a flat surface; furthermore, which part of the residues serve as 'identifier' for the surface."

First, Applicants respectfully submit that there is no requirement in the claim that the surface defined by these residues be "flat".

Second, reference to a "surface structurally defined by poliovirus RNA-dependent RNA polymerase residues 342 and 349 or residues at corresponding positions in a RNA-dependent RNA polymerase" in claim 3 is meant to refer to a particular portion of Interface I of an RNA-dependent RNA polymerase, using the amino acid sequence of poliovirus RNA-dependent RNA

polymerase as a reference point. Figure 2C shows the structure of Interface I in poliovirus RNA-dependent RNA polymerase, including the position of residues 342 and 349.

"surface defined by . . . corresponding positions thereof"

The Office has rejected claim 3 for recitation of "surface identify by . . . corresponding positions thereof" on the grounds that "corresponding positions thereof" is not defined.

Applicants respectfully note that the phrase "corresponding positions" is indeed defined in the specification at paragraph [0043] to mean:

> the position of an amino acid in a peptide . . . corresponds to the same position in the sequence of the conserved binding surface of different viral polymerases, i.e. different but related positive strand virus such as a picornavirus and a flavivirus. Thus a residue in a specific position in Interface I of a poliovirus will have a "corresponding position" in the conserved interface of a different picornavirus, a flavivirus, etc.

binding of pharmacophore

The Office further rejected claim 3 on the grounds that it is not clear "whether the pharmacophore is supposed to bind the indicated . . . residues themselves, or the surface defined thereby."

Applicants respectfully submit that this distinction drawn by the Office is not understood. As noted above, a "surface structurally defined by poliovirus RNA-dependent RNA polymerase residues 342 and 349 or residues at corresponding positions in a RNA-dependent RNA polymerase" in claim 3 is meant to refer to a particular portion of Interface I of an RNA-dependent RNA polymerase, using the amino acid sequence of poliovirus RNA-dependent RNA polymerase as a reference point.

Conclusion

Withdrawal of the rejections of claim 3 under §112, ¶2 is respectfully requested.

Claims 15 and 16

The Office has rejected claim 15 for recitation of "disruption of a plurality of positive stand virus". Claim 15 has been amended to recite "disruption of a plurality of positive stand viruses". Therefore, in view of the amendment to the claim, the rejection is rendered moot.

REJECTIONS UNDER §112, ¶1 – "WRITTEN DESCRIPTION"

Claims 1-3 and 14-16 were rejected under §112, ¶1 on the grounds that the claims contain subject matter not adequately described in the specification. The Office Action states that

> The claims are drawn to a pharmacophore that binds to surface defined by residues 342 and 349 of RNA-polymerase. Specification does not describe any pharmacophore that binds, specifically, to said residues of RNA-polymerase. Example 10 (pages 47-49) does describe peptide SEQ ID No. 5 which does disrupt RNA-polymerase functions. However, there is no evidence that said polypeptide belongs to the genus as claimed, i.e, that it does bind to the specified residues 342 and 349 of RNA-polymerase.

(Office Action, page 4).

This rejection is respectfully traversed.

As described in the specification (see, e.g., paragraph [00105]), Interface I interactions involve 21 direct amino acid side chain interactions, at least 5 water mediated interactions and one direct backbone-backbone hydrogen bond. The interactions at Interface I can be divided into two distinct regions. The first region (at the top of Interface I in Figure 2C) centers around L446 which extends from the surface of one polymerase molecule and into a hydrophobic pocket in the adjacent polymerase molecule. The hydrophobic pocket of this second molecule is formed from two separate peptide loops which immediately precede and follow the conserved poliovirus polymerase C motif. Numerous direct as well as water mediated interactions also occur between the residues in these two loops and the residues flanking L446.

The second region of interaction at Interface I involves two α -helices (the C-terminal α-helix of one molecule and the motif D α -helix of the second molecule) that pack together at an angle of approximately 90°. Almost all of the surface exposed amino acid side chains on both of these helices interact across this interface. These interactions include R455 from one helix which hydrogen bonds with D349 from the helix of the adjacent polymerase molecule as well as L342 from one molecule, which packs against a hydrophobic patch on the other polerase molecule.

Applicants submit that the inhibitor peptide is reasonably expected to interact with the portion of Interface I having the residues 342 and 349 because the inhibitor is designed based on the sequence of the alpha-helix that interacts with this region in the polymerase. The peptide described in the application as exemplary of pharmacophores that disrupt polymerase binding at Interface I – KPHKCTFEGCRKSYSRSTNLRRHLNSH (SEQ ID NO:5) –was designed to mimic the continuous α-helix at Interface I. See, Example 10, paragraphs [00156] – [00164], particularly paragraph [00158]. In other words, the α-helix this peptide was designed to mimic an amino acid sequence present in the polymerase subunit that interacts with the region of Interface I having residues 342 and 349. Thus the peptide of SEQ ID NO:5 does indeed provide an example of a pharmacophore of the present claims.

Once provided with the knowledge of the three-dimensional structure of RNA-dependent RNA polymerase, and further when provided with the inventors' discovery that a peptide designed to mimic the α-helix at Interface I can inhibit polymerase function, the ordinarily skilled artisan can design additional inhibitors using this information.

Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER §112, ¶1 – "ENABLEMENT"

Claims 1-3 and 13-16 were rejected under §112, ¶1 on the grounds that the specification is not enabling for making of the product as claimed. This rejection is respectfully traversed

As Applicants understand it, this rejection flows from the rejection of the claims under §112, ¶2. Specifically, the rejection is based on the assertion that the claim language means that the pharmacophore binds not particular residues of RNA polymerase, but rather binds a surface "defined by" the residues.

This rejection arises since the Office has taken the position that the term "surface structurally defined by . . . residues 342 and 349" is not clear. Based on this, the Office asserts that it is not clear how to make products that satisfy the claimed structural limitations. Further, the Office asserts that although the specification reviews known methods of drug modeling, this description does not address the issue of undefined structure to which the pharmacophore is to bind. The Office again asserts that there is no evidence the peptide of SEQ IDNO:5 – which does disrupt RNA-polymerase function – binds to the specified residues 342 and 349 of RNA-polymerase.

Applicants respectfully submit that this rejection is addressed in view of the clarification to the claims as described above in the context of the rejections under §112, ¶2. For example, reference to a "surface structurally defined by poliovirus RNA-dependent RNA polymerase residues 342 and 349 or residues at corresponding positions in a RNA-dependent RNA polymerase" in claim 3 is meant to refer to a particular portion of Interface I of an RNA-dependent RNA polymerase, using the amino acid sequence of poliovirus RNA-dependent RNA polymerase as a reference point. Figure 2C shows the structure of Interface I in poliovirus RNA-dependent RNA polymerase, including the position of residues 342 and 349.

As to the binding of the peptide of SEQ ID NO:5 to this region of Interface I, this has been addressed above in the context of the written description rejection under §112, ¶1. In short, the peptide of SEQ ID NO:5 was designed to mimic mimic an amino acid sequence present in the polymerase subunit that interacts with the region of Interface I having residues 342 and 349. Thus the peptide of SEQ ID NO:5 does indeed provide an example of a pharmacophore of the present claims.

There is ample information available regarding the structure of Interface I in poliovirus RNA-dependent RNA polymerase, as well as the structure of Interface I among other viral RNA-dependent RNA polymerases in view of its conserved nature across viruses. Methods of molecular modeling for production of pharmacophores that interact with a structure of interest are also known. Thus, once provided with the inventors' discovery that, for example, disruption of RNA-dependent RNA polymerase interactions at Interface I, e.g., by binding of a pharmacophore at this site, inhibits polymerase activity, the ordinarily skilled artisan can readily make such compounds.

Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER §102

Claims 1-3 and 14-16 have been rejected as anticipated by Sergio et al. (US 6,492,423). This rejection is respectfully traversed.

Sergio et al. is cited for its disclosure of diketoacids that inhibit viral polymerases, particular RNA-dependent RNA polymerase. The rejection is based on the Office's position that since these diketoacids inhibit RNA-dependent RNA-polymerase, the are inherently capable of binding to the RNA-dependent RNA-polymerase. The Office assumes that, in the absence of evidence to the contrary, the inhibitors of Sergio et al. bind to the RNA-dependent RNA-polymerase in the manner required by the instant claims, and shifts the burden to Applicants to show a novel or unobvious difference between the claimed product and that of Sergio et al.

The pharmacophores of the current claims are designed to disrupt interactions at Interface I, particularly at the region defined by residues 342 and 349.

In contrast, the Sergio et al patent is for a group of compounds that target the active sites of RNA-dependent RNA polymerases. Specifically, Sergio et al. col. 1, lines 30-41 states:

DISCLOSURE OF THE INVENTION

The present inventors have discovered that a range of diketoacids have utility as enzyme inhibitors and, in particular, as polymerase inhibitors and more particularly as inhibitors of hepatitis C NS5 RNA-dependent RNA polymerase, HBV DNA-dependent RNA polymerase and HIV DNA-dependent DNA polymerase. Their investigations indicate that these compounds may act by interfering with the binding of phosporyl groups at the active site of the enzyme and may, therefore, have broad application in inhibiting enzymes involved in the transfer of phospboryl groups.

Sergio et al. describes several compounds of different formulas that fall within the diketoacid class. Also at col. 89, line 61- 90, Sergio et al. states:

> While not wishing to be bound by any particular theory, the present inventors hypothesize that the diketoacid fragment of the compounds of the present invention inhibits RNA dependent polymerase activity by providing an "active site anchor" and interacting with divalent metal cations (Mg^{2+}, Mn^{2+}) required for polymerase activity. The ring system found on the left hand side of the molecule can
>
> apparently be modified in order to build specificity towards a giver polymerase.

The crystal structure of RNA-dependent RNA polymerase shows that the binding surfaces at Interface I (as well as the binding surfaces at Interface II) are distinct from the active site targeted by Sergio et al. See, e.g., Lyle et al. (2002) *Science* 296:2218-2222 (copy attached).

Therefore, the inhibitors of Sergio et al. are not inhibitors of the claimed invention, as they are not pharmacophores that interact with Interface I of a viral RNA-dependent RNA polymerase, e, g., by binding to a surface structurally defined by poliovirus RNA-dependent RNA polymerase residues 342 and 349.

Withdrawal of this rejection is thus respectfully requested.

REJECTIONS UNDER §103

Claim 13 has been rejected as being obvious in view of Sergio et al. (US 6,492,423). This rejection is respectfully traversed.

As noted above, the Sergio et al. patent discloses a group of compounds that target the active sites of RNA-dependent RNA polymerases. In contrast, the pharmacophores of the current claims are designed to disrupt interactions at Interface I, particularly at the region defined by residues 342 and 349. Since, the Sergio et al. patent does not teach this element of the invention, the cited reference fails to render claim 13 obvious.

Withdrawal of this rejection is thus respectfully requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-193.

Respectfully submitted,
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Date: Nov. 30, 2004

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Enclosure(s): Lyle et al. (2002) *Science* 296:2218-2222

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